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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,494	12/13/2000	Nikolich Zugich	MSK.P-042	2225

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,494	ZUGICH ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *5-8,10 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,11-14 and 16* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on 6/22/05, PROSECUTION IS HEREBY REOPENED. The following new grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below: Christina Chan

2. Claims 1-16 are pending. Claims 5-8, 10 and 15 remain withdrawn from consideration as not directed to the elected invention.

Claims 1-4, 9, 11-14 and 16 are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 12, 13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification

does not convey to the artisan that the Applicant had possession at the time of invention of the claimed inventions.

The instant claims encompass: (1) the method recited in instant claims 1-4, 12 and 13 wherein the therapeutic antigen (*i.e.*, the MHC binding peptide) is not MHC class I-restricted, and (2) a method for inducing a cellular immune response to a target peptide that is non-immunogenic in a mammalian subject and that is expressed by tumor cells of the said subject, comprising administering a therapeutic antigen SSIEFARL from herpes simplex glycoprotein B, said therapeutic antigen being a heteroclitic peptide based upon the target peptide SEIEFARL present in the glycoprotein B sequence (claim 16).

There is no disclosure for inducing a cellular immune response with anything other than an MHC class I binding heteroclitic peptide. There is no written description in the specification that the target peptide SEIEFARL recited in instant claim 16 is expressed on any tumor cell in any mammalian subject or that the target peptide is non-immunogenic and there is no description of inducing a therapeutically effective cellular immune response to the said target peptide in any mammalian subject except in mice that were inoculated with target peptide transfected RMA-S B lymphoma cells, and therefore conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention.

The specification discloses that the therapeutic antigen can be constructed based upon the immunodominant sequence 498-505 of the herpes simplex virus glycoprotein B (page 9 at lines 7-13). The specification further discloses that the target peptide served as a *model* of a tumor antigen of viral origin and that it binds poorly to the murine MHC class I molecule H-2Kb. The specification discloses that the target peptide could not sensitize EL-4 target cells *in vitro* for lysis by CTL elicited by peptide immunization *in vivo*, the target cells presumably loaded with endogenous peptides and the control being non-target peptide pulsed cells rather than a control using another peptide/CTL combination. The specification discloses that the target peptide was expressed by transfection into RMA-S B lymphoma cells along with transfection of an ERIS sequence to bypass the transporter defect in the said cells, and that three CTL lines derived from B6 mice by immunization with the target antigen were able to lyse the transfected cells *in vitro*, indicating a cross-reaction for the target antigen of the CTL produced against the heteroclitic therapeutic peptide. The specification further discloses that mice immunized with the heteroclitic or parental (target) peptide were challenged with the target peptide transfected RMAS cells, and that the mice immunized with the heteroclitic (therapeutic) peptide were protected from tumor challenge, or that genetic immunization with DNA encoding the heteroclitic peptide induced rejection of transferred RMA-S B lymphoma cells (Example 1).

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed composition recited in the instant claims.

5. Claims 1-4, 12, 13 and 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing an immune response comprising administering the heteroclitic peptide SSIEFARL to a mouse that has been injected with tumor cells transfected with the SEIEFARL peptide, or for inducing the said immune response to a class I MHC binding peptide, does not reasonably provide enablement for the claimed method for inducing an immune response in a mammal possessing tumor cells comprising administering the heteroclitic peptide SSIEFARL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims encompass: (1) a method for inducing a cellular immune response to a target peptide that is non-immunogenic in a mammalian subject and that is expressed by tumor cells of the said subject, comprising administering a therapeutic antigen SSIEFARL from herpes simplex glycoprotein B, said therapeutic antigen being a heteroclitic peptide based upon the target peptide SEIEFARL present in the glycoprotein B sequence (claim 16), (2) the said method wherein the MHC binding peptide, *i.e.*, the therapeutic antigen, is not binding MHC class I.

There is no disclosure in the specification that the target peptide SEIEFARL recited in instant claim 16 is expressed on any tumor cell in any mammalian subject or that the said target peptide is non-immunogenic, nor that the target or therapeutic peptides recited in the instant claims bind any MHC except MHC class I.

The specification discloses that the therapeutic antigen can be constructed based upon the immunodominant sequence 498-505 of the herpes simplex virus glycoprotein B (page 9 at lines 7-13). The specification further discloses that the target peptide served as a *model* of a tumor antigen of viral origin and that it binds poorly to the murine MHC class I molecule H-2Kb. The specification discloses that the target peptide could not sensitize EL-4 target cells *in vitro* for lysis by CTL elicited by peptide immunization *in vivo*, the target cells presumably loaded with endogenous peptides and the control being non-target peptide pulsed cells rather than a control using another peptide/CTL combination. The specification discloses that the target peptide was expressed by transfection into RMA-S B lymphoma cells along with transfection of an ERIS sequence to bypass the transporter defect in the said cells, and that three CTL lines derived from B6 mice by immunization with the target antigen were able to lyse the transfected cells

in vitro, indicating a cross-reaction for the target antigen of the CTL produced against the heteroclitic therapeutic peptide. The specification further discloses that mice immunized with the heteroclitic or parental (target) peptide were challenged with the target peptide transfected RMAS cells, and that the mice immunized with the heteroclitic (therapeutic) peptide were protected from tumor challenge, or that genetic immunization with DNA encoding the heteroclitic peptide induced rejection of transferred RMA-S B lymphoma cells (Example 1).

Evidentiary reference Lipford et al teach that using a heteroclitic peptide that binds to MHC class I for immunization *in vivo* based upon a parent peptide is only feasible provided that the target peptide is expressed on the tumor target cell and if CTL produced against the heteroclitic peptide is cross-reactive with the parent peptide. There is insufficient guidance in the specification as to how to practice the method of the instant invention. There is no disclosure in the specification as to using the peptide SSIEFARL to induce a therapeutically effective cellular immune response in any mammal except in mice injected with peptide-transfected B lymphoma cells, nor wherein the mammal expresses a non-immunogenic target peptide that is SEIEFARL, nor wherein the MHC binding therapeutic antigen is not binding MHC class I. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4, 9, 11-14 and 16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "thereby inducing a therapeutically effective cellular immune response" because it is not clear what is meant, i.e., what the metes and bounds of the limitation are.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al (Immunology 84(2), 1995, 298-303, IDS reference) in view of Urban et al (Crit. Rev. Immunol. 1997, 17: 387-397), US 5,662,907 and Erlich (Human Immunol. 1997, 54: 104-116).

Lipford et al teach a method of inducing an immune response by administering a heteroclitic peptide (i.e., a "therapeutic antigen") YIFAFRDL (E6.1 I2) which was altered from HPV E6 peptide YDFAFRDL at position 2 to improve peptide MHC class I H-2K^b binding affinity, and to render it capable of inducing an immune response (*i.e.,* "immune recognition domain binds to a cytotoxic T cell") whereas it had not been immunogenic prior to alteration (especially introduction and last paragraph on page 302). The peptides are 8 amino acid residues in length, *i.e.*, "from 8 to 14 amino acids". Lipford et al further teach that HPV types 16 and 18 are associated with 90% of cervical carcinomas (page 298 at column 2, first sentence of the last paragraph). Lipford et al teach that the E6 protein is from HPV type 16 (especially page 299 at column 1, first full sentence). Lipford et al teach that the target peptide YDFAFRDL had poor H-2K^b binding affinity and was not capable of inducing an immune response after peptide inoculation, *i.e.,* it was non-immunogenic in a mouse upon *in vivo* vaccination (*i.e.,* a mammalian subject) (especially page 299 at column 1, second full sentence). Lipford et al teach that CTL elicited *in vivo* by injection of the heteroclitic peptide or "therapeutic antigen" into mice were able to lyse a syngeneic tumor cell line transformed with the E6 gene, implying that the E6.1 peptide was processed and presented, *i.e.,* the E6.1 peptide is generated and expressed on the cell surface and that the steady-state quantity of E6.1 peptide presented was sufficient to activate the E6.1 I2-induced CTL to lyse the transfected tumor cells (especially abstract and page 300 at column 1 last paragraph and continuing on to page 301 through the first full paragraph of column 1). Lipford et al further teach that the said CTL were able to lyse cells pulsed exogenously with both the parental wild type peptide E6 and the heteroclitic E6.1 I2 peptide, and that such cross-reactivity of CTL clones to peptides modified at single buried positions, i.e., those that are MHC contact residues, is well documented (especially *ibid* and Discussion paragraph 2 at column 2 on page 301). Lipford et al teach that their data show that MHC class I stabilization, *i.e.,* binding of peptide to class I MHC with higher affinity, is an indicator of immunogenicity and that cross-reactivity can be induced by peptides with point substitutions in non-T cell receptor interacting positions (especially page 300 at column 2 at lines 16-20). Lipford et al teach that in an HPV-infected cell, it must be considered that any peptide capable of binding MHC class I such as E6.1 may be brought to the surface of cells for presentation, albeit at reduced levels, and that this low steady-state level of peptide presentation may be detectable by activated CTL yet fail to activate naïve T cells, and in the instant case, the E6.1 peptide was processed and presented at sufficient quantities for CTL recognition (especially page 301 at column 2, second paragraph). Lipford et al teach that their approach is relevant to the design of subunit vaccines to virally induced tumors, regardless of the antigenicity of the desired peptide epitope, provided processing and presentation by target cells occurs (especially abstract and last paragraph of article), *i.e.*, Lipford et al teach that an

immunogenic version of a non-immunogenic peptide can be designed by improving the binding affinity to MHC class I and that the altered immunogenic version of the peptide may be used for inducing a cellular immune response in a mouse or human if the non-immunogenic peptide is expressed on the target cells in the mouse or human and if the CTL that are induced cross-react with the non-immunogenic peptide.

Lipford et al do not teach that the target peptide YDFAFRDL is expressed by tumor cells of a mammalian subject, nor do they teach any other peptides expressed by tumor cells in a mammalian subject, nor do they exemplify administering heteroclitic peptides that are based upon a target tumor-expressed peptide.

Urban et al teach using mass spectrometry for determining naturally processed and expressed peptides that bind to MHC molecules on the surface of cells. Urban et al further teach immunizing a subject with these peptides, peptides altered with lipids to increase stability *in vivo*, or nucleic acid molecules encoding the peptides (see entire article).

US 5,662,907 discloses that immunogenic HLA class I binding tumor peptides when injected into humans could induce anti-tumor peptide CTL capable of lysing tumor targets (see entire reference, especially abstract and column 17 at lines 31-45).

Erlich teaches that class I MHC presented peptides on tumor cells are usually non-immunogenic (especially abstract, page 108 at column 2 at the last sentence of the first full paragraph, and the second and third paragraphs of column 1 on page 109).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the approach of Lipford et al, i.e., making heteroclitic peptides based upon non-immunogenic parent peptides from tumor antigens such as taught by Erlich et al or Lipford et al, for parent peptides that are present on the surface of tumor cells in mammalian subjects as determined by the mass spectrometry using the method taught by Urban et al, and to have used the resulting heteroclitic peptides to induce an immune response to the parent (target peptide) in the mammal as taught by Lipford et al similarly to the method of induction of CTL using immunogenic peptides disclosed by US 5,662,907.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer by using immunogenic versions of non-immunogenic target peptides because Lipford et al teach that their approach is relevant to the design of subunit vaccines to virally induced tumors, regardless of the antigenicity of the desired peptide epitope or non-immunogenicity of the target peptide, provided processing and presentation by target cells occurs, and Lipford et al teach that their data show that MHC class I stabilization, *i.e.*, binding of peptide to class I MHC with higher affinity, is an indicator of immunogenicity and that cross-reactivity can be induced by peptides with point substitutions in non-T cell receptor interacting positions, Erlich et

al teach that tumor peptides presented by MHC class I molecules are usually non-immunogenic, and Urban et al teach methods of determining which peptides are present on the surface of cells bound to MHC class I molecules, and Lipford et al and US 5,662,907 teach or disclose inducing a therapeutically effective immune response by *in vivo* administration of peptide, that is, using it as a vaccine. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because Lipford et al teach that a non-immunogenic peptide from HPV E6 protein, associated with cervical cancer, could be made immunogenic in the same subjects by increasing its binding affinity to MHC class I, and that CTL produced *in vivo* in response to peptide inoculation was capable of lysing a tumor cell line transformed with the E6 gene that processed and presented the parental non-immunogenic peptide, *i.e.,* immunization using the altered immunogenic peptide provided an effective immune response against the tumor cells *ex vivo*, and Lipford et al teach that their approach is applicable to making an altered peptide version of any subimmunogenic tumor associated peptide and using it as a vaccine.

10. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al (Immunology 84(2), 1995, 298-303, IDS reference) in view of Urban et al (Crit. Rev. Immunol. 1997, 17: 387-397), US 5,662,907 and Erlich (Human Immunol. 1997, 54: 104-116) as applied to claims 1, 2, and 9 above, and further in view of Anderson et al (J. Exp. Med. 174(8): 489-492, 1991, IDS reference) and Yewdell et al (J. Immunol. 152: 1163-1170, 1994, IDS reference).

The combination of Lipford et al, Urban et al, US 5,662,907 and Erlich has been discussed above, hereafter referred to as "the combined references".

The combined references do not teach the claimed method wherein the therapeutic antigen further comprises an ER trafficking signal.

Anderson et al teach a peptide preceded by an ER translocation signal (i.e., an ER sorting/trafficking signal) and the importance of peptide transport into the ER for expression of class I MHC peptide complexes for induction of an immune response (see entire reference).

Yewdell et al teach antigenic peptides carboxy terminal to an ER insertion sequence, and the importance of the ER insertion sequence in delivering the peptide to the ER for peptide/MHC class I expression at the cell surface (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a heteroclitic peptide connected to an ER sorting/trafficking signal as taught by Anderson et al and Yewdell et al to be used in the method taught by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more efficiently induce an immune response to the heteroclitic peptide in the method of the combined references given the teachings of Anderson et al and Yewdell et al of the importance of peptide transport into the ER for expression of class I MHC peptide complexes at the cell surface.

11. Claims 11, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al (Immunology 84(2), 1995, 298-303, IDS reference) in view of Urban et al (Crit. Rev. Immunol. 1997, 17: 387-397), US 5,662,907 and Erlich (Human Immunol. 1997, 54: 104-116) as applied to claims 1, 2, and 9 above, and further in view of Tourdot et al (J. Immunol. 159: 2391-2398, 1997, IDS reference) and Naftzger et al (PNAS USA 93: 14809-14814, 1996).

The combination of Lipford et al, Urban et al, US 5,662,907 and Erlich has been discussed above, hereafter referred to as "the combined references".

The combined references do not teach the claimed method wherein the target peptide is a self-peptide expressed in normal and tumor tissues of a mammalian subject, such as gp75, nor wherein the MHC class I molecule is HLA-*0201.

Tourdot et al teach that vaccination with immunodominant peptides is not always efficient in eliminating virus or tumors, that in the case of tumors, the majority of tumor antigens that are targets of tumor immunotherapy are self proteins and the CTL repertoire against their immunodominant epitopes must be tolerized. Tourdot et al further teach that anti-tumor CTL developed in melanoma patients are usually directed against peptides exhibiting low MHC binding affinity that is a characteristic of subdominant peptides. Tourdot et al teach that in these situations, vaccination with subdominant peptides will be the way to induce antitumor or antiviral protection. Torudot et al teach that since these low affinity peptides can not recruit a specific CTL repertoire, these peptides could be used for vaccination only if they become highly immunogenic, such as by producing chimeric peptides composed by amino acid residues from a high affinity MHC class I binding peptide at the MHC contact positions, and amino acid residues from *nonimmunogenic* low MHC class I affinity binding peptides at the TCR contact positions. Tourdot et al teach that their approach using chimeric or heteroclitic peptides can be applied to other MHC molecules to recruit subdominant tumor peptide-specific CTL, and further teach that HLA-A2.1, *i.e.*, HLA-A*0201, is an MHC class I molecule. Tourdot et al teach that recruitment of the large and high avidity CTL repertoire specific for low MHC affinity subdominant tumor epitopes by the chimeric or heteroclitic peptides should lead to a better antitumor protective immunity than recruitment of the incomplete and low avidity CTL repertoire for the high affinity dominant peptides (especially abstract, page2391, first paragraph of pages 2392, last paragraph on page 2397).

Naftzger et al teach that mouse gp75, present on melanocytes as well as on malignant melanoma, is non-immunogenic in mice, both for antibody production and for CTL production, and that active immunization using human g75 or syngeneic gp75 produced in insect cells could provide tumor protection in the form of autoantibodies (especially abstract and introduction section).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have identified peptides from the non-immunogenic gp75 melanoma antigen taught by Naftzger et al, or of any other potential self peptides on tumor cells such as those taught by Tourdot et al, that bind to class I MHC, including to HLA-A*0201 taught by Tourdot et al, on the surface of melanoma cells using the method of the combined references and to have created heteroclitic analogs of the said peptides using the methodology taught by the combined reference or taught by Tourdot et al and to have administered them *in vivo* in order to induce a CTL-mediated anti-gp75 immune response as taught for heteroclitic peptides in the method of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to induce a CTL-mediated tumor response to gp75 or to another non-immunogenic antigen and to peptides derived from such antigens, because the method of the combined references teach administration of heteroclitic peptides based upon non-immunogenic tumor-expressed peptides and Tourdot et al and Naftzger et al teach non-immunogenic peptides or proteins that are present on tumors and Naftzger et al teach gp75 which is expressed on both tumor and normal tissues, and because Tourdot teach that their approach is applicable to other MHC class I molecules such as HLA-A*0201.

12. Claims 1, 2, 9, 11, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al (Immunology 84(2), 1995, 298-303, IDS reference) in view of Urban et al (Crit. Rev. Immunol. 1997, 17: 387-397), US 5,662,907, Erlich (Human Immunol. 1997, 54: 104-116), Tourdot et al (J. Immunol. 159: 2391-2398, 1997, IDS reference) and Naftzger et al (PNAS USA 93: 14809-14814, 1996).

Lipford et al teach a method of inducing an immune response by administering a heteroclitic peptide (i.e., a "therapeutic antigen") YIFAFRDL (E6.1 I2) which was altered from HPV E6 peptide YDFAFRDL at position 2 to improve peptide MHC class I H-2K^b binding affinity, and to render it capable of inducing an immune response (*i.e.,* "immune recognition domain binds to a cytotoxic T cell") whereas it had not been immunogenic prior to alteration (especially introduction and last paragraph on page 302). The peptides are 8 amino acid residues in length, *i.e.*, "from 8 to 14 amino acids". Lipford et al further teach that HPV types 16 and 18 are associated with 90% of cervical carcinomas (page 298 at column 2, first sentence of the last paragraph). Lipford et al teach that the E6 protein is from HPV type 16 (especially page 299 at column 1, first full sentence). Lipford et al teach that the target peptide YDFAFRDL had poor H-2K^b

binding affinity and was not capable of inducing an immune response after peptide inoculation, *i.e.,* it was non-immunogenic in a mouse upon *in vivo* vaccination (*i.e.,* a mammalian subject) (especially page 299 at column 1, second full sentence). Lipford et al teach that CTL elicited *in vivo* by injection of the heteroclitic peptide or "therapeutic antigen" into mice were able to lyse a syngeneic tumor cell line transformed with the E6 gene, implying that the E6.1 peptide was processed and presented, *i.e.,* the E6.1 peptide is generated and expressed on the cell surface and that the steady-state quantity of E6.1 peptide presented was sufficient to activate the E6.1 I2-induced CTL to lyse the transfected tumor cells (especially abstract and page 300 at column 1 last paragraph and continuing on to page 301 through the first full paragraph of column 1). Lipford et al further teach that the said CTL were able to lyse cells pulsed exogenously with both the parental wild type peptide E6 and the heteroclitic E6.1 I2 peptide, and that such cross-reactivity of CTL clones to peptides modified at single buried positions, i.e., those that are MHC contact residues, is well documented (especially *ibid* and Discussion paragraph 2 at column 2 on page 301). Lipford et al teach that their data show that MHC class I stabilization, *i.e.,* binding of peptide to class I MHC with higher affinity, is an indicator of immunogenicity and that cross-reactivity can be induced by peptides with point substitutions in non-T cell receptor interacting positions (especially page 300 at column 2 at lines 16-20). Lipford et al teach that in an HPV-infected cell, it must be considered that any peptide capable of binding MHC class I such as E6.1 may be brought to the surface of cells for presentation, albeit at reduced levels, and that this low steady-state level of peptide presentation may be detectable by activated CTL yet fail to activate naïve T cells, and in the instant case, the E6.1 peptide was processed and presented at sufficient quantities for CTL recognition (especially page 301 at column 2, second paragraph). Lipford et al teach that their approach is relevant to the design of subunit vaccines to virally induced tumors, regardless of the antigenicity of the desired peptide epitope, provided processing and presentation by target cells occurs (especially abstract and last paragraph of article), *i.e.*, Lipford et al teach that an immunogenic version of a non-immunogenic peptide can be designed by improving the binding affinity to MHC class I and that the altered immunogenic version of the peptide may be used for inducing a cellular immune response in a mouse or human if the non-immunogenic peptide is expressed on the target cells in the mouse or human and if the CTL that are induced cross-react with the non-immunogenic peptide.

Lipford et al do not teach that the target peptide Y**D**FAFRDL is expressed by tumor cells of a mammalian subject, nor do they teach any other peptides expressed by tumor cells in a mammalian subject, nor do they exemplify administering heteroclitic peptides that are based upon a target tumor-expressed peptide. Lipford et al do not teach the claimed method wherein the target peptide is a self-peptide expressed in normal and tumor tissues of a mammalian subject, such as gp75, nor wherein the MHC class I molecule is HLA-*0201.

Urban et al teach using mass spectrometry for determining naturally processed and expressed peptides that bind to MHC molecules on the surface of cells. Urban et al further teach immunizing a subject with these peptides, peptides altered with lipids to increase stability *in vivo*, or nucleic acid molecules encoding the peptides (see entire article).

US 5,662,907 discloses that immunogenic HLA class I binding tumor peptides when injected into humans could induce anti-tumor peptide CTL capable of lysing tumor targets (see entire reference, especially abstract and column 17 at lines 31-45).

Erlich teaches that class I MHC presented peptides on tumor cells are usually non-immunogenic (especially abstract, page 108 at column 2 at the last sentence of the first full paragraph, and the second and third paragraphs of column 1 on page 109).

Tourdot et al teach that vaccination with immunodominant peptides is not always efficient in eliminating virus or tumors, that in the case of tumors, the majority of tumor antigens that are targets of tumor immunotherapy are self proteins and the CTL repertoire against their immunodominant epitopes must be tolerized. Tourdot et al further teach that anti-tumor CTL developed in melanoma patients are usually directed against peptides exhibiting low MHC binding affinity that is a characteristic of subdominant peptides. Tourdot et al teach that in these situations, vaccination with subdominant peptides will be the way to induce antitumor or antiviral protection. Torudot et al teach that since these low affinity peptides can not recruit a specific CTL repertoire, these peptides could be used for vaccination only if they become highly immunogenic, such as by producing chimeric peptides composed by amino acid residues from a high affinity MHC class I binding peptide at the MHC contact positions, and amino acid residues from *nonimmunogenic* low MHC class I affinity binding peptides at the TCR contact positions. Tourdot et al teach that their approach using chimeric or heteroclitic peptides can be applied to other MHC molecules to recruit subdominant tumor peptide-specific CTL, and further teach that HLA-A2.1, *i.e.*, HLA-A*0201, is an MHC class I molecule. Tourdot et al teach that recruitment of the large and high avidity CTL repertoire specific for low MHC affinity subdominant tumor epitopes by the chimeric or heteroclitic peptides should lead to a better antitumor protective immunity than recruitment of the incomplete and low avidity CTL repertoire for the high affinity dominant peptides. Tourdot et al exemplify administering heteroclitic peptides to mice is an effective method of inducing protective immunity (especially abstract, page2391, first paragraph of pages 2392, last paragraph on page 2397).

Naftzger et al teach that mouse gp75, present on melanocytes as well as on malignant melanoma, is non-immunogenic in mice, both for antibody production and for CTL production, and that active immunization using human g75 or syngeneic gp75 produced in insect cells could provide tumor protection in the form of autoantibodies (especially abstract and introduction section).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the approach of Lipford et al and of Tourdot et al, *i.e.,* making heteroclitic peptides, including those that bind to HLA-A*0201 taught by Tourdot et al, based upon non-immunogenic parent peptides from tumor antigens such as taught by Erlich et al or Lipford et al or Naftzger et al, for parent peptides that are present on the surface of tumor cells in mammalian subjects as determined by the mass spectrometry using the method taught by Urban et al, and to have used the resulting heteroclitic peptides to induce an immune response to the parent peptide (*i.e*, the target peptide) in the mammal as taught by Lipford et al similarly to the method of induction of CTL using immunogenic peptides disclosed by US 5,662,907.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer by using immunogenic versions of non-immunogenic target peptides because Lipford et al and Tourdot et al teach that their approach is relevant to the design of subunit vaccines to tumors or viruses, regardless of the antigenicity of the desired peptide epitope or non-immunogenicity of the target peptide, provided processing and presentation by target cells occurs, Urban et al teach methods of determining which peptides are present on the surface of cells bound to MHC class I molecules, and Lipford et al teach that their data show that MHC class I stabilization, *i.e.,* binding of peptide to class I MHC with higher affinity, is an indicator of immunogenicity and that cross-reactivity can be induced by peptides with point substitutions in non-T cell receptor interacting positions, Erlich et al teach that tumor peptides presented by MHC class I molecules are usually non-immunogenic, Naftzger et al teach that the mouse self-and-tumor protein gp75 is non-immunogenic, and Lipford et al and US 5,662,907 teach or disclose, respectively, inducing a therapeutically effective immune response by *in vivo* administration of peptide, that is, using it as a vaccine.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because Erlich teaches that most MHC class I binding tumor associated peptides are non-immunogenic, such as mouse gp75 taught by Naftzger et al, and Lipford et al teach that a non-immunogenic peptide from HPV E6 protein, associated with cervical cancer, could be made immunogenic in the same subjects by increasing its binding affinity to MHC class I, and that CTL produced *in vivo* in response to peptide inoculation was capable of lysing a tumor cell line transformed with the E6 gene that processed and presented the parental non-immunogenic peptide, *i.e.,* immunization using the altered immunogenic peptide provided an effective immune response against the tumor cells *ex vivo*, and Lipford et al teach that their approach is applicable to making an altered peptide version of any subimmunogenic tumor associated peptide and using it as a vaccine provided the non-immunogenic peptide is expressed on tumor cells, Urban et al teach a method of determining if peptides are expressed on cells bound to MHC class I, and Tourdot et al teach that administration of heteroclitic peptides is an effective means of protective immunity, and US 5,662,907

discloses inducing a therapeutically effective immune response by *in vivo* administration of peptide.

13. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al (Immunology 84(2), 1995, 298-303, IDS reference) in view of Urban et al (Crit. Rev. Immunol. 1997, 17: 387-397), US 5,662,907, Erlich (Human Immunol. 1997, 54: 104-116), Tourdot et al (J. Immunol. 159: 2391-2398, 1997, IDS reference) and Naftzger et al (PNAS USA 93: 14809-14814, 1996) as applied to claims 1, 2, 9, 11, 12 and 13 above, and further in view of Anderson et al (J. Exp. Med. 174(8): 489-492, 1991, IDS reference) and Yewdell et al (J. Immunol. 152: 1163-1170, 1994, IDS reference).

The combination of Lipford et al, Urban et al, US 5,662,907, Erlich, Tourdot et al and Naftzger et al has been discussed above, hereafter referred to as "the combined references".

The combined references do not teach the claimed method wherein the therapeutic antigen further comprises an ER trafficking signal.

Anderson et al teach a peptide preceded by an ER translocation signal (i.e., an ER sorting/trafficking signal) and the importance of peptide transport into the ER for expression of class I MHC peptide complexes for induction of an immune response (see entire reference).

Yewdell et al teach antigenic peptides carboxy terminal to an ER insertion sequence, and the importance of the ER insertion sequence in delivering the peptide to the ER for peptide/MHC class I expression at the cell surface (see entire reference).
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a heteroclitic peptide connected to an ER sorting/trafficking signal as taught by Anderson et al and Yewdell et al to be used in the method taught by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more efficiently induce an immune response to the heteroclitic peptide in the method of the combined references given the teachings of Anderson et al and Yewdell et al of the importance of peptide transport into the ER for expression of class I MHC peptide complexes at the cell surface.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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